APPENDIX D

Esophageal Cancer

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Esophageal Cancer

General Information

Note: Separate PDQ summaries on Prevention of Esophageal Cancer and Screening for Esophageal Cancer are also available.

Note: Estimated new cases and deaths from esophageal cancer in the United States in 2005:[1]

- New cases: 14,520.
- Deaths: 13,570.

The incidence of esophageal cancer has risen in recent decades, coinciding with a shift in histologic type and primary tumor location.[2][3] Adenocarcinoma of the esophagus is now more prevalent than squamous cell carcinoma in the United States and western Europe, with most tumors located in the distal esophagus. The cause for the rising incidence and demographic alterations is unknown.

While risk factors for squamous cell carcinoma of the esophagus have been identified (e.g., tobacco, alcohol, diet), the risk factors associated with esophageal adenocarcinoma are less clear.[3] The presence of Barrett's

esophagus is associated with an increased risk of developing adenocarcinoma of the esophagus, and chronic reflux is considered the predominant cause of Barrett's metaplasia. The results of a population-based, case-controlled study from Sweden strongly suggest that symptomatic gastroesophageal reflux is a risk factor for esophageal adenocarcinoma. The frequency, severity, and duration of reflux symptoms were positively correlated with increased risk of esophageal adenocarcinoma.[4]

Esophageal cancer is a treatable disease, but it is rarely curable. The overall 5-year survival rate in patients amenable to definitive treatment ranges from 5% to 30%. The occasional patient with very early disease has a better chance of survival. Patients with severe dysplasia in distal esophageal Barrett's mucosa often have in situ or even invasive cancer within the dysplastic area. Following resection, these patients usually have excellent prognoses.

Primary treatment modalities include surgery alone or chemotherapy with radiation therapy. Combined modality therapy (i.e., chemotherapy plus surgery, or chemotherapy and radiation therapy plus surgery) is under clinical evaluation. Effective palliation may be obtained in individual cases with various combinations of surgery, chemotherapy, radiation therapy, stents,[5] photodynamic therapy,[6][7][8] and endoscopic therapy with Nd:YAG laser.[9]

One of the major difficulties in allocating and comparing treatment modalities for patients with esophageal cancer is the lack of precise preoperative staging. Standard noninvasive staging modalities include computed tomography (CT) of the chest and abdomen, and endoscopic ultrasound (EUS). The overall tumor depth staging accuracy of EUS is 85% to 90%, as compared with 50% to 80% for CT; the accuracy of regional nodal staging is 70% to 80% for EUS and 50% to 70% for CT.[10][11] EUS-guided fine-needle aspiration (FNA) for lymph node staging is under prospective evaluation; 1 retrospective series reported a 93% sensitivity and 100% specificity of regional nodal staging with EUS-FNA.[12] Thoracoscopy and laparoscopy have been used in esophageal cancer staging at some surgical centers.[13][14][15] An intergroup trial reported an increase in positive lymph node detection to 56% of 107 evaluable patients using thoracoscopy/laparoscopy, from 41% (using noninvasive staging tests, e.g., CT, magnetic resonance imaging, EUS) with no major complications or deaths.[16] Noninvasive positron emission tomography using the radiolabeled glucose analog 18-F-fluorodeoxy-D-glucose for preoperative staging of esophageal cancer is under clinical evaluation and may be useful in detecting stage IV disease.[17][18][19][20]

Gastrointestinal stromal tumors can occur in the esophagus and are usually benign. (Refer to the PDQ summary on Adult Soft Tissue Sarcoma Treatment for more information.)

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14. Sugarbaker DJ, Jaklitsch MT, Liptay MJ Thoracoscopic staging and surgical therapy for esophageal cancer. Chest 107 (6 Suppl): 218S-223S, 1995. Related Entries
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16. Krasna MJ, Reed CE, Nedzwiecki D, et al. CALGB 9380: a prospective trial of the feasibility of thoracoscopy/laparoscopy in staging esophageal cancer. Ann Thorac Surg 71 (4): 1073-9, 2001. Related Entries
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emission tomography for assessment of the response to induction radiochemotherapy in locally advanced oesophageal cancer. Ann Oncol 13 (3): 361-8, 2002. Related Entries

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Cellular Classification

Fewer than 50% of esophageal cancers are squamous cell carcinomas. Adenocarcinomas, typically arising in Barrett's esophagus, account for at least 50% of malignant lesions, and the incidence of this histology appears to be rising. Barrett's esophagus contains glandular epithelium cephalad to the esophagogastric junction.

Three different types of glandular epithelium can be seen:

- Metaplastic columnar epithelium.
- Metaplastic parietal cell glandular epithelium within the esophageal wall.
- Metaplastic intestinal epithelium with typical goblet cells.

Dysplasia is particularly likely to develop in the intestinal type mucosa.

Gastrointestinal stromal tumors can occur in the esophagus and are usually benign. (Refer to the PDQ summary on Adult Soft Tissue Sarcoma Treatment for more information.)

Stage Information

The stage determines whether the intent of the therapeutic approach will be curative or palliative. The American Joint Committee on Cancer (AJCC) has designated staging by TNM classification.[1]

TNM definitions

Primary tumor (T)

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor invades lamina propria or submucosa
- T2: Tumor invades muscularis propria.
- T3: Tumor invades adventitia
- T4: Tumor invades adjacent structures

Regional lymph nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis

Distant metastasis (M)

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis
    - Tumors of the lower thoracic esophagus:
        - M1a: Metastasis in celiac lymph nodes
        - M1b: Other distant metastasis
    - Tumors of the midthoracic esophagus:
        - M1a: Not applicable
        - M1b: Nonregional lymph nodes and/or other distant metastasis
    - Tumors of the upper thoracic esophagus:
        - M1a: Metastasis in cervical nodes
        - M1b: Other distant metastasis

For tumors of the midthoracic esophagus, use only M1b because these tumors with metastases in nonregional lymph nodes have equally poor prognoses as do those with metastases in other distant sites.

AJCC stage groupings

Stage 0

- Tis, N0, M0

Stage I

- T1, N0, M0

Stage IIA

- T2, N0, M0
- T3, N0, M0

Stage IIB

- T1, N1, M0
- T2, N1, M0

Stage III

- T3, N1, M0
- T4, any N, M0

Stage IV

- Any T, any N, M1

Stage IVA

- Any T, any N, M1a

Stage IVB

- Any T, any N, M1b

The current staging system for esophageal cancer is based largely on retrospective data from the Japanese Committee for Registration of Esophageal Carcinoma. It is most applicable to patients with squamous cell carcinomas of the upper-third and middle-third of the esophagus, as opposed to the increasingly common distal esophageal and gastroesophageal junction adenocarcinomas.[2] In particular, the classification of involved abdominal lymph nodes as M1 disease has been criticized. The presence of positive abdominal lymph nodes does not appear to carry as grave a prognosis as metastases to distant organs.[3] Patients with regional and/or celiac axis lymphadenopathy should not necessarily be considered to have unresectable disease due to metastases. Complete resection of the primary tumor and appropriate lymphadenectomy should be attempted when possible.

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2. Iizuka T, Isono K, Kakegawa T, et al. Parameters linked to ten-year survival in Japan of resected esophageal carcinoma. Japanese Committee for Registration of Esophageal Carcinoma Cases. Chest 96 (5): 1005-11, 1989. Related Entries
3. Korst RJ, Rusch VW, Venkatraman E, et al. Proposed revision of the staging classification for esophageal cancer. J Thorac Cardiovasc Surg 115 (3): 660-69; discussion 669-70, 1998. Related Entries

Treatment Option Overview

Note: Some citations in the text of this section are followed by a level of evidence. The PDQ editorial boards use a formal ranking system to help the reader judge the strength of evidence linked to the reported results of a therapeutic strategy. (Refer to the PDQ summary on Levels of Evidence for more information.)

The prevalence of Barrett's metaplasia in adenocarcinoma of the esophagus suggests that Barrett's esophagus is a premalignant condition. Strong consideration should be given to resection in patients with high-grade dysplasia in the setting of Barrett's metaplasia. Endoscopic surveillance of patients with Barrett's metaplasia may detect adenocarcinoma at an earlier stage more amenable to curative resection.[1] The survival rate of patients with esophageal cancer is poor. Asymptomatic small tumors confined to the esophageal mucosa or submucosa are detected only by chance. Surgery is the treatment of choice for these small tumors. Once symptoms are present (e.g., dysphagia, in most cases), esophageal cancers have usually invaded the muscularis propria or beyond and may have metastasized to lymph nodes or other organs.

In the presence of complete esophageal obstruction without clinical evidence of systemic metastasis, surgical excision of the tumor with mobilization of the stomach to replace the esophagus has been the traditional means of relieving the dysphagia. In the United States, the median age of patients who present with esophageal cancer is 67 years.[2] The results of a retrospective review of 505 consecutive patients who were operated on by a single surgical team over 17 years found no difference in the perioperative mortality, median survival, or palliative benefit of esophagectomy on dysphagia when the group of patients older than 70 years were compared to their younger peers.[3][Level of evidence: 3iiA, 3iiB] All of the patients in this series were selected for surgery on the basis of potential operative risk. Age alone should not determine therapy for patients with potentially resectable disease.

The optimal surgical procedure is controversial. One approach advocates transhiatal esophagectomy with anastomosis of the stomach to the cervical esophagus. A second approach advocates abdominal mobilization of the stomach and transthoracic excision of the esophagus with anastomosis of the stomach to the upper thoracic esophagus or the cervical esophagus. One study concluded that transhiatal esophagectomy was associated with lower morbidity than transthoracic esophagectomy with extended en bloc lymphadenectomy; however, median overall disease-free and quality-adjusted survival did not differ significantly.[4] Similarly, no differences in long-term quality of life (QOL) using validated QOL instruments have been reported.[5] In patients with partial esophageal obstruction, dysphagia may, at times, be relieved by placement of an expandable metallic stent [6] or by radiation therapy if the patient has disseminated disease or is not a candidate for surgery. Alternative methods of relieving dysphagia have been reported, including laser therapy and electrocoagulation to destroy intraluminal tumor.[7] [8][9][10]

Surgical treatment of resectable esophageal cancers results in 5-year survival rates of 5% to 30%, with higher survival rates in patients with early-stage cancers. This is associated with a <10% operative mortality rate.[11] In an attempt to avoid this perioperative mortality and to relieve dysphagia, definitive radiation therapy in combination with chemotherapy has been studied. An Intergroup randomized trial, Radiation Therapy Oncology Group (RTOG) 85-01, of chemotherapy and radiation therapy versus radiation therapy alone resulted in an improvement in 5-year survival for the combined modality group (27% vs. 0%).[12][Level of evidence: 1iiA] Eight-year follow-up of this trial demonstrated an overall survival rate of 22% for patients receiving chemoradiation therapy.[12] An Eastern Cooperative Oncology Group trial of 135 patients showed that chemotherapy plus radiation provided a better 2-year survival rate than radiation therapy alone,[13] which was similar to that shown in the Intergroup trial.[12][Level of evidence: 1iiA] In an attempt to improve upon the results of RTOG 85-01, Intergroup 0123 (RTOG 94-05) randomized 236 patients with localized esophageal tumors to chemoradiation with high-dose radiation therapy (64.8 Gy) and 4 monthly cycles of fluorouracil (5-FU) and cisplatin versus conventional-dose radiation therapy (50.4 Gy) and the same chemotherapy schedule.[14] Although originally designed to accrue 298 patients, this trial was closed in 1999 after a planned interim analysis showed that it was statistically unlikely that there would be any advantage to using high-dose radiation. At 2 years median follow-up, no statistical differences were observed between the high-dose and conventional-dose radiation therapy arms in median survival (13 months vs. 18 months), 2-year survival (31% vs. 40%), or local/regional failures (56% vs. 52%).[14][Level of evidence: 1iiA]

Phase III trials have compared preoperative concurrent chemoradiotherapy to surgery alone for patients with esophageal cancer.[15][16][17][Level of evidence: 1iiA] A multicenter prospective randomized trial in which preoperative combined chemotherapy (i.e., cisplatin) and radiation therapy (37 Gy in 3.7 Gy fractions) followed by surgery was compared to surgery alone in patients with squamous cell carcinoma showed no improvement in overall survival and a significantly higher postoperative mortality (12% vs. 4%) in the combined modality arm.[15] In patients with adenocarcinoma of the esophagus, a single-institution phase III trial demonstrated a modest survival benefit (16 months vs. 11 months) for patients treated with induction chemoradiotherapy consisting of 5-FU, cisplatin, and 40 Gy (2.67 Gy fractions) plus surgery over resection alone.[16] Finally, a single-institution trial randomized patients (75% with adenocarcinoma) to 5-FU, cisplatin, vinblastine, and radiation therapy (1.5 Gy twice daily to a total of 45 Gy) plus resection versus esophagectomy alone.[17] At a median follow-up of more than 8 years, there was no significant difference between the surgery alone and combined modality therapy with respect to median survival (17.6 months vs. 16.9 months), overall survival (16% vs. 30% at 3 years), or disease-free survival (16% vs. 28% at 3 years). On the basis of the results of these 3

prospective randomized trials, preoperative chemoradiotherapy should still be considered under clinical evaluation.

Cisplatin-based chemoradiation regimens containing paclitaxel with or without 5-FU are under clinical evaluation in the United States.[18][19] A phase II single-arm trial reported that a paclitaxel-cisplatin combination administered preoperatively with radiation is well tolerated and showed pathological complete response rates and complete resection rates similar to those of other trials containing 5-FU chemotherapy regimens.[20][Level of evidence: 3iiiDiii]

The effects of preoperative chemotherapy have been evaluated in 2 randomized trials.[21][22][Level of evidence: 1iiA]. An Intergroup trial randomized 440 patients with local and operable esophageal cancer of any cell type to 3 cycles of preoperative 5-FU and cisplatin followed by surgery and 2 additional cycles of chemotherapy versus surgery alone. After a median follow-up of 55 months, there were no significant differences between the chemotherapy/surgery and surgery-alone groups in median survival (14.9 months and 16.1 months, respectively) or 2-year survival (35% and 37%, respectively). The addition of chemotherapy did not increase the morbidity associated with surgery. The Medical Research Council Oesophageal Cancer Working Party randomized 802 patients with resectable esophageal cancer also of any cell type to 2 cycles of preoperative 5-FU and cisplatin followed by surgery versus surgery alone. At a median follow-up of 37 months, median survival was significantly improved in the preoperative chemotherapy arm (16.8 months vs. 13.3 months with surgery alone; difference 3.5 months; 95% confidence interval [CI] 1-6.5 months), as was 2-year overall survival (43% and 34% respectively; difference 9%; 95% CI 3-14 months). The interpretation of the results from both of these trials is challenging, as T or N staging was not reported prerandomization and radiation could be offered at the discretion of the treating oncologist. Therefore, preoperative chemotherapy should still be considered under clinical evaluation.

Two randomized trials have shown no significant overall survival benefit for postoperative radiation therapy over surgery alone.[23][24][Level of evidence: 1iiA] All newly diagnosed patients should be considered candidates for therapies and clinical trials comparing various treatment modalities.

Special attention to nutritional support is indicated in any patient undergoing treatment of esophageal cancer. (Refer to the PDQ summary on Nutrition in Cancer Care for more information.)

The designations in PDQ that treatments are â€œstandardâ€□ or â€œunder clinical evaluationâ€□ are not to be used as a basis for reimbursement determinations.

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21. Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med 339 (27): 1979-84, 1998. Related Entries
22. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 359 (9319): 1727-33, 2002. Related Entries
23. Ténière P, Hay JM, Fingerhut A, et al. Postoperative radiation therapy does not increase survival after curative resection for squamous cell carcinoma of the middle and lower esophagus as shown by a multicenter controlled trial. French University Association for Surgical Research. Surg Gynecol Obstet 173 (2): 123-30, 1991. Related Entries
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Stage 0 Esophageal Cancer

Stage 0 squamous esophageal cancer is rarely seen in the United States, but surgery has been used for this stage of cancer.[1][2]

1. Rusch VW, Levine DS, Haggitt R, et al. The management of high grade dysplasia and early cancer in Barrett's esophag us. A multidisciplinary problem. Cancer 74 (4):

1225-9, 1994. Related Entries
2. Heitmiller RF, Redmond M, Hamilton SR Barrett's esophagus with high-grade dysplasia. An indication for prophylactic esophagectomy. Ann Surg 224 (1): 66-71, 1996. Related Entries

Stage I Esophageal Cancer

Standard treatment options:

- Surgery.

Treatment options under clinical evaluation:

- Clinical trials as outlined in the treatment option overview. Information about ongoing clinical trials is available from the NCI Web site.

Stage II Esophageal Cancer

Standard treatment options:

- Surgery.

Treatment options under clinical evaluation:

- Chemotherapy plus radiation therapy with or without subsequent surgery.[1][2][3] Information about ongoing clinical trials is available from the NCI Web site.

1. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 281 (17): 1623-7, 1999. Related Entries
2. Herskovic A, Al-Sarraf M Combination of 5-Fluorouracil and Radiation in Esophageal Cancer. Semin Radiat Oncol 7 (4): 283-290, 1997. Related Entries
3. Ajani JA, Komaki R, Putnam JB, et al. A three-step strategy of induction chemotherapy then chemoradiation followed by surgery in patients with potentially resectable carcinoma of the esophagus or gastroesophageal junction. Cancer 92 (2): 279-86, 2001. Related Entries

Stage III Esophageal Cancer

Standard treatment options:

- Surgical resection of T3 lesions.

Treatment options under clinical evaluation:

- Chemotherapy plus radiation therapy with or without subsequent surgery.[1][2] Information about ongoing clinical trials is available from the NCI Web site.

1. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 281 (17): 1623-7, 1999. Related Entries
2. Herskovic A, Al-Sarraf M Combination of 5-Fluorouracil and Radiation in Esophageal Cancer. Semin Radiat Oncol 7 (4): 283-290, 1997. Related Entries

Stage IV Esophageal Cancer

At diagnosis, approximately 50% of patients with esophageal cancer will have metastatic disease and will be candidates for palliative therapy.[1]

Standard treatment options:

1. Endoscopic -placed stents to provide palliation of dysphagia.[2]
2. R adiation therapy with or without intraluminal intubation and dilation.
3. I ntraluminal brachytherapy to provide palliation of dysphagia.[3][4]
4. Nd:YAG e ndoluminal tumor destruction or electrocoagulation.[5]
5. C hemotherapy has provided partial responses for patients with metastatic distal esophageal adenocarcinomas.[6][7] [8]

Treatment options under clinical evaluation:

Many agents are active in esophageal cancer. Objective response rates of 30% to 60% and median survivals of <1 year are commonly reported with platinum-based combination regimens with fluorouracil, taxanes, topoisomerase inhibitors, hydroxyurea, or vinorelbine.[1][8][9]

- Clinical trials evaluating single-agent or combination chemotherapy. Information about ongoing clinical trials is available from the NCI Web site.

1. Enzinger PC, Ilson DH, Kelsen DP Chemotherapy in esophageal cancer. Semin Oncol 26 (5 Suppl 15): 12-20, 1999. Related Entries
2. Baron TH Expandable metal stents for the treatment of cancerous obstruction of the gastrointestinal tract. N Engl

J Med 344 (22): 1681-7, 2001. Related Entries
3. Sur RK, Levin CV, Donde B, et al. Prospective randomized trial of HDR brachytherapy as a sole modality in palliation of advanced esophageal carcinoma--an International Atomic Energy Agency study. Int J Radiat Oncol Biol Phys 53 (1): 127-33, 2002. Related Entries
4. Gaspar LE, Nag S, Herskovic A, et al. American Brachytherapy Society (ABS) consensus guidelines for brachytherapy of esophageal cancer. Clinical Research Committee, American Brachytherapy Society, Philadelphia, PA. Int J Radiat Oncol Biol Phys 38 (1): 127-32, 1997. Related Entries
5. Bourke MJ, Hope RL, Chu G, et al. Laser palliation of inoperable malignant dysphagia: initial and at death. Gastrointest Endosc 43 (1): 29-32, 1996. Related Entries
6. Waters JS, Norman A, Cunningham D, et al. Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomized trial. Br J Cancer 80 (1-2): 269-72, 1999. Related Entries
7. Ross P, Nicolson M, Cunningham D, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) With epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. J Clin Oncol 20 (8): 1996-2004, 2002. Related Entries
8. Taïeb J, Artru P, Baujat B, et al. Optimisation of 5-fluorouracil (5-FU)/cisplatin combination chemotherapy with a new schedule of hydroxyurea, leucovorin, 5-FU and cisplatin (HLFP regimen) for metastatic oesophageal cancer. Eur J Cancer 38 (5): 661-6, 2002. Related Entries
9. Conroy T, Etienne PL, Adenis A, et al. Vinorelbine and cisplatin in metastatic squamous cell carcinoma of the oesophagus: response, toxicity, quality of life and survival. Ann Oncol 13 (5): 721-9, 2002. Related Entries

Recurrent Esophageal Cancer

All recurrent esophageal cancer patients present difficult problems in palliation. All patients, whenever possible, should be considered candidates for clinical trials as outlined in treatment overview.

Standard treatment options:

- Palliative use of any of the standard therapies, including supportive care.

Treatment options under clinical evaluation:

- Clinical trials as outlined in the treatment option overview. Information about ongoing clinical trials is

available from the NCI Web site.

Changes to This Summary (04/13/2005)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

General Information

Added van Westreenen et al. as reference 20.

Treatment Option Overview

Added text to state that no differences in long-term quality of life (QOL) using validated QOL instruments have been reported (cited deBoer et al. as reference 5).

More Information

About PDQ

- PDQ® - NCI's Comprehensive Cancer Database.
  - Full description of the NCI PDQ database.

Additional PDQ Summaries

- PDQ® Cancer Information Summaries: Adult Treatment
  - Treatment options for adult cancers.
- PDQ® Cancer Information Summaries: Pediatric Treatment
  - Treatment options for childhood cancers.
- PDQ® Cancer Information Summaries: Supportive Care
  - Side effects of cancer treatment, management of cancer-related complications and pain, and psychosocial concerns.
- PDQ® Cancer Information Summaries: Screening/Detection (Testing for Cancer)
  - Tests or procedures that detect specific types of cancer.
- PDQ® Cancer Information Summaries: Prevention
  - Risk factors and methods to increase chances of preventing specific types of cancer.
- PDQ® Cancer Information Summaries: Genetics
  - Genetics of specific cancers and inherited cancer syndromes, and ethical, legal, and social concerns.
- PDQ® Cancer Information Summaries: Complementary and Alternative Medicine
  - Information about complementary and alternative forms of treatment for patients with cancer.

Important:

This information is intended mainly for use by doctors and other health care professionals. If you have questions about this topic, you can ask your doctor, or call the Cancer Information Service at **1-800-4-CANCER (1-800-422-6237)**.

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